These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi Drug substance(s): Docetaxel	Study Identifiers: NCT00261703 Study code: XRP6976F_2503
Title of the study: Randomized phase III trial comparing induction chemotherapy with Cisplatin /5-FU (PF) or Docetaxel /Cisplatin/5-FU (TPF) plus chemoradiotherapy (CRT) versus CRT alone as first-line treatment of unresectable locally advanced head and neck cancer (LAHNC)	
Study center(s): 21 Centers from Spain	
Study period: Date first subject enrolled: 23/Dec/2002 Date last subject completed: 19/Jul/2010	
Phase of development: III	
Objectives: The primary end point was time to treatment failure (TTF) for IC (Induction Chemotherapy), TPF-CRT and TP-CRT vs no ICT, only CRT; secondary endpoints included locoregional control (LRC) rate and safety.	
Methodology: Randomized, open-label phase III trial	

Number of subjects:		Planned: 439
		Randomized: 439
		Treated: TPF-CRT 153 ; TP-CRT 156 ; CRT alone 118 pts.
Evaluated:	Efficacy:	Per Protocol: TPF-CRT 113 ; TP-CRT 113 ; CRT alone 118
		Per ITT: TPF-CRT 155 ; TP-CRT 155 ; CRT alone 128
	Safety:	TPF-CRT 153 ; TP-CRT 155 ; CRT alone 118

Diagnosis and criteria for inclusion:

Inclusion Criteria

- Unresectable LAHNC
  - Primary site carcinoma of the oral cavity, oropharynx, hypopharynx or larynx
  - Stage III or IV (M0)
  - ≥1 measurable lesion
- ECOG 0-1
- Age ≥ 18 years
- Life expectancy ≥ 6 months
- Adequate haematological, hepatic and renal functions

Exclusion Criteria

- Pregnant woman
- Paranasal sinuses,nasopharynx and nasal cavity tumours
- Previous chemo or radiotherapy tumour treatment
- Peripheral neuropathy grade ≥ 2
- Loss weight ≥ 10% in the last three months

Study treatments

Investigational medicinal product(s):

Formulation: Docetaxel 75 mg/m², Day 1 ; Cisplatin 75 mg/m², Day 1 ; 5-FU 750 mg/m²/day, Days 1 to 5 (cIV)

Route(s) of administration: IV administration

Noninvestigational medicinal product(s)

Formulation: Cisplatin 100 mg/m², Day 1 ; 5-FU 1000 mg/m²/day, Days 1 to 5 (cIV)

Route(s) of administration: IV administration

Duration of treatment:

TP and TPF: 16 weeks, in two parts: ICT (Induction chemotherapy), 3 cycles 21 days (9 weeks) followed by chemoradiotherapy (7weeks).

CRT: treatment duration 7 weeks.

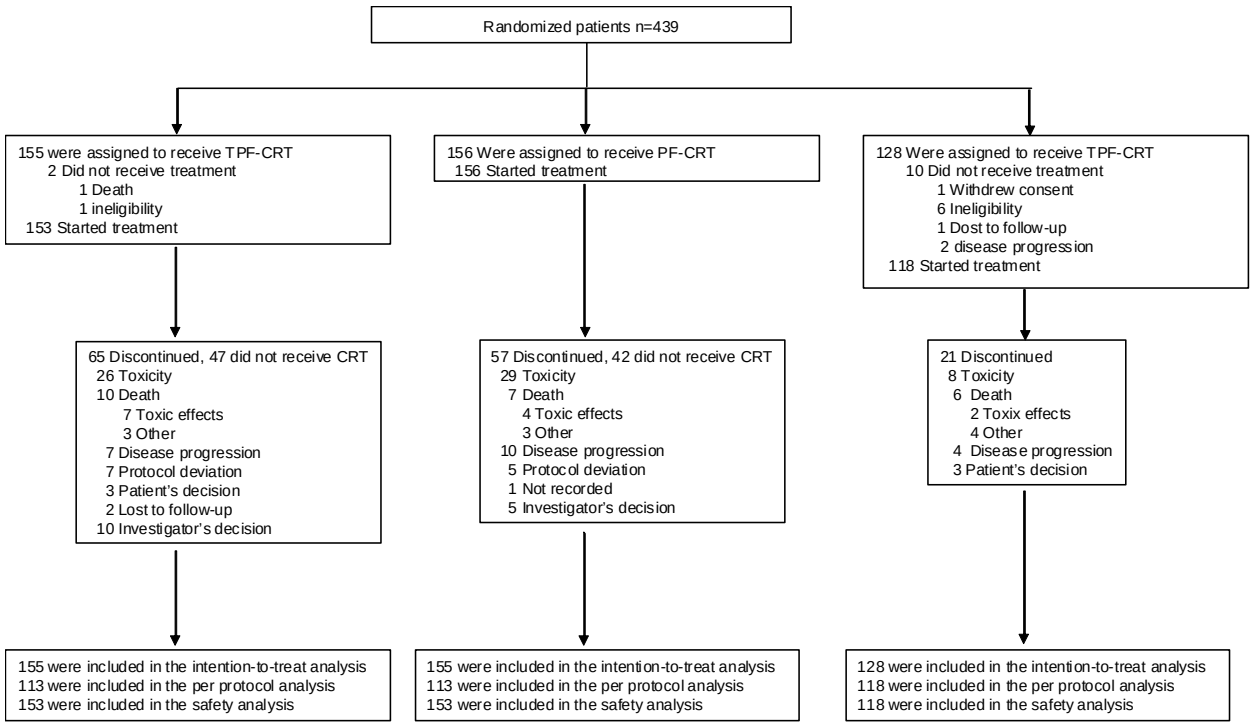
Duration of observation: 24 Months

Criteria for evaluation:

Efficacy Evaluable: Patients with at least 1 cycle of CRT and/or ICT; all early progressions and deaths due to tumor are also considered evaluable for efficacy analysis

Safety: All patients with at least 1 dose of study treatment

Flow of trial participants



Efficacy: Patients characteristics at base line

	TPF N: 155	PF N: 156	CRT N: 128
Median Age	57 (35-78)	58 (36-85)	55 (25-79)
Male/female	93%	92%	89%
ECOG 0/1	8/92%	13/87%	8/92%
Primary tumor site Oropharynx Hypophariynx Larynx Oral Cavity	 41% 19% 19% 21%	 43% 18% 17% 22%	 43% 19% 18% 20%

	TPF N: 155	PF N: 156	CRT N: 128
TN stage T4N0	 19%	 10%	 17%
T4N1	18%	16%	21%
T4N2	43%	41%	32%
T4N3	0%	8%	6%
Total T4	80%	75%	76%

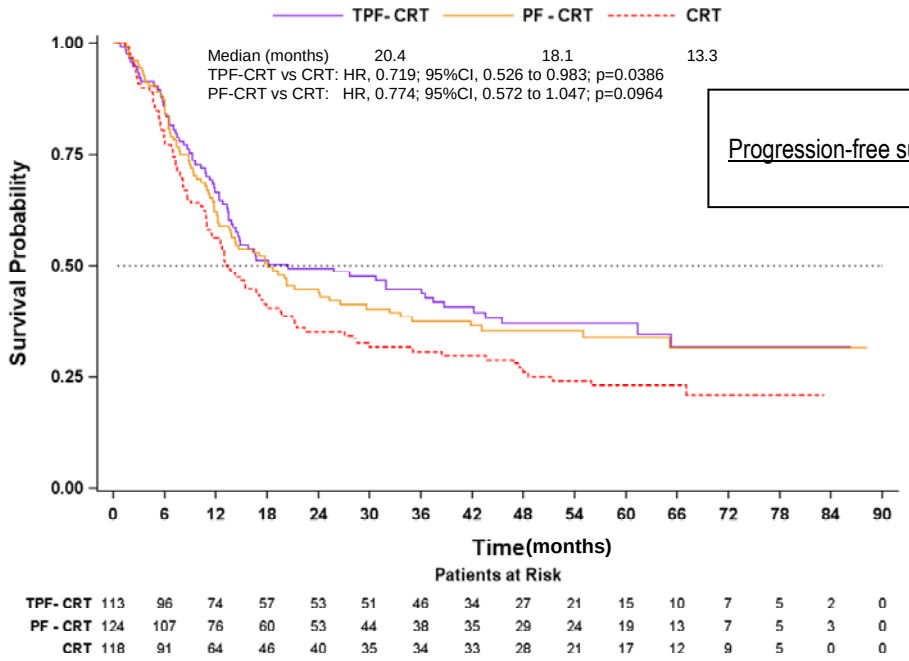
Compliance of program

	TPF	PF	CRT
Median cycles ICT	3	3	
Dose reduction ICT	14%	92%	89%
Dose Intensity Mg/m2/w. median	Platin 0,98 5FU 0,98 TXT0,98	Platin 0,91 5FU 0,91	Platin 0,97
Median duration CRT	9w	8w	8w
Median dose or CRT	70 Gy	70 Gy	69 Gy
Median cycles cisplatin/RT	3	3	3

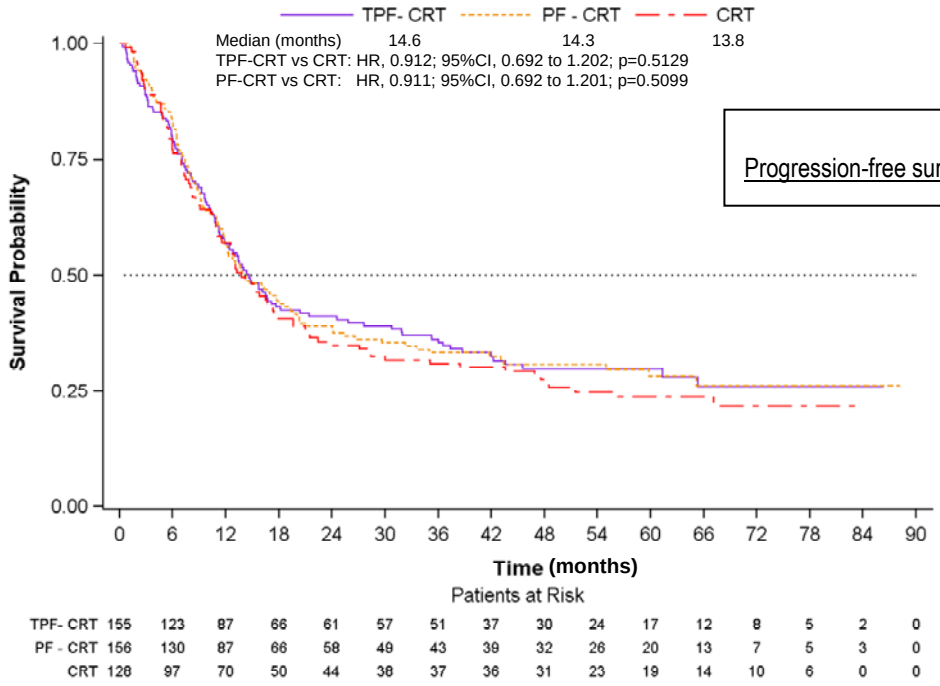
	TPF	PF	CRT
Delay of cisplatin/RT %	39	42	38
Causes of delay %	Non haematological: 50	Non haematological: 50	Non haematological: 50
Reduction of cisplatin/RT %	19	17	8
Dose intensity of cisplatin/RT Mg/m2/w median	0.88	0.90	0.97
Compliance of full program %	52	61	91

Tumor responses

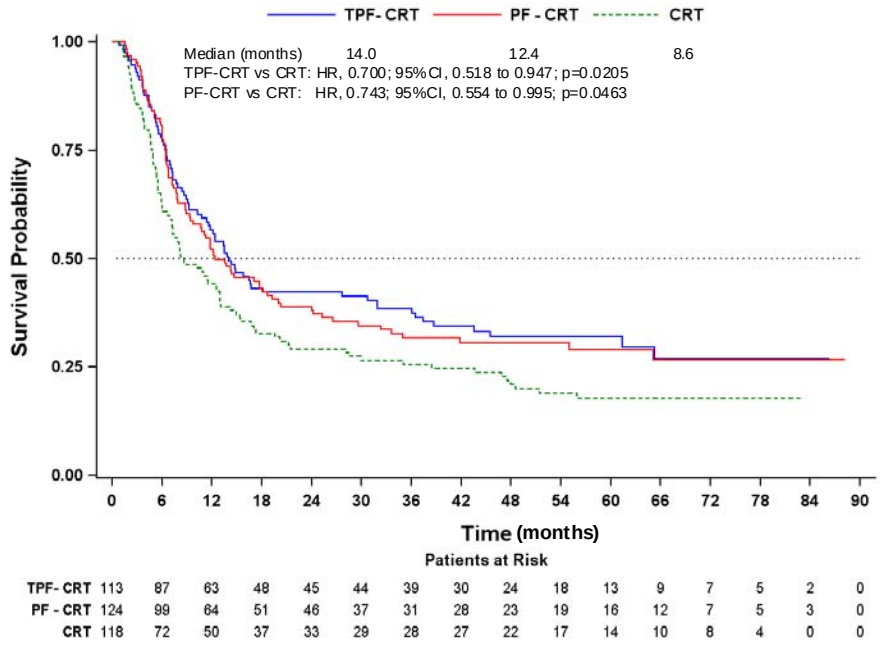
	ICT period			All study treatment periods		
	TPF	PF	CRT	TPF-CRT	PF-CRT	CRT
ITT population						
Overall, n (%)	101 (77.7)	108 (77.7)	NA	115 (87.1)	115 (81.6)	95 (90.5)
Complete response, n (%)	40 (30.8)	40 (28.8)	NA	76 (57.6)	76 (53.9)	51 (48.6)
Partial response, n (%)	61 (46.9)	68 (48.9)	NA	39 (29.6)	39 (27.7)	44 (41.9)
PP population						
Overall, n (%)	87 (79.8)	98 (81.0)	NA	101 (91.0)	105 (85.4)	95 (90.5)
Complete response, n (%)	35 (32.1)	38 (31.4)	NA	71 (64.0)	74 (60.2)	51 (48.6)
Partial response, n (%)	52 (47.7)	60 (49.6)	NA	30 (27.0)	31 (25.2)	44 (41.9)

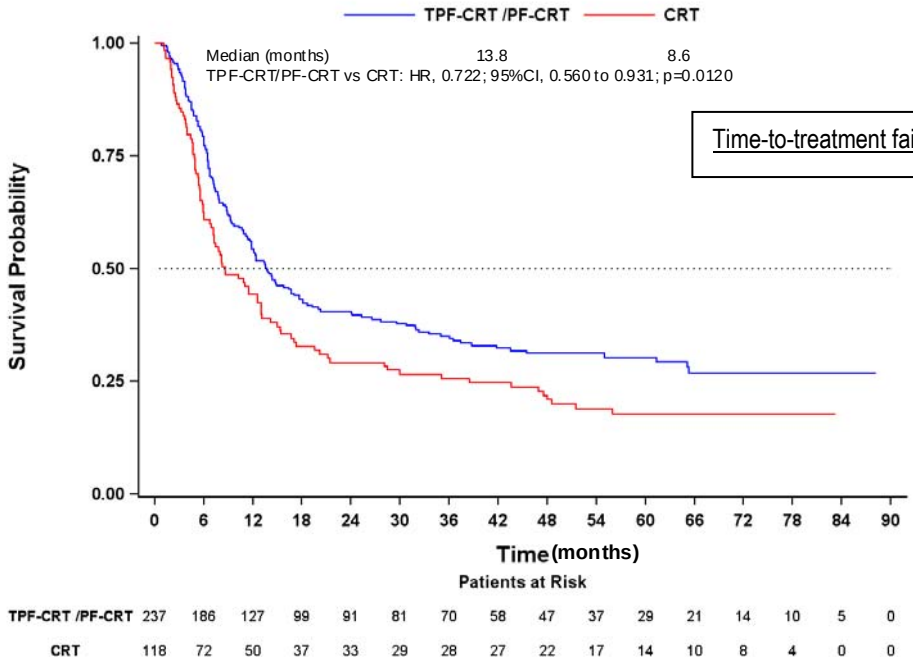


Progression-free survival (PP population)



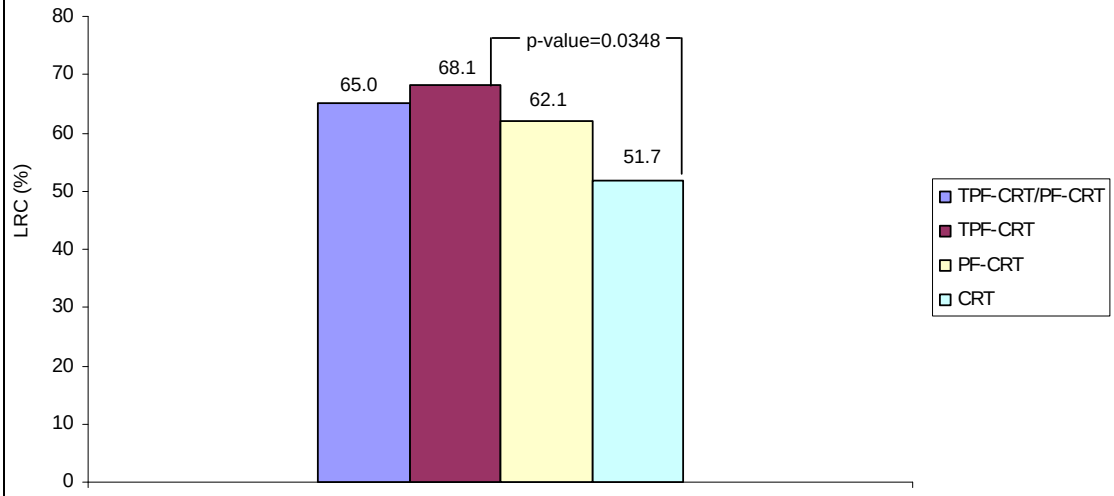
Progression-free survival (ITT population)



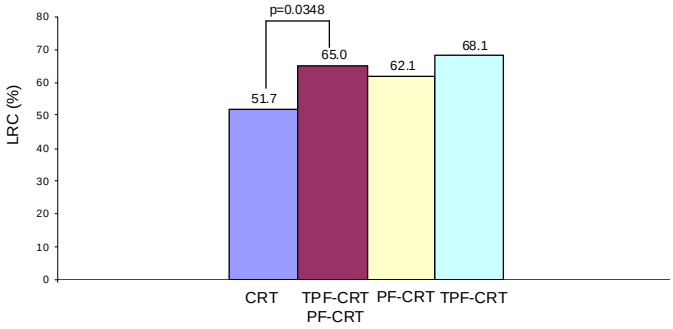


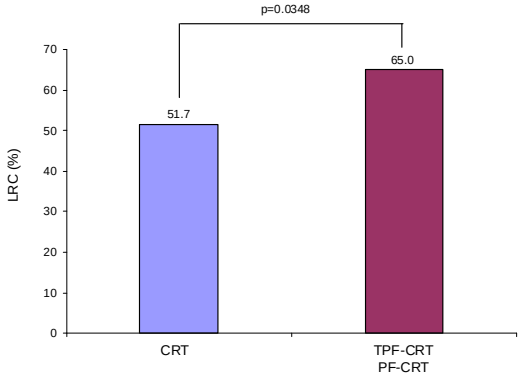
Time-to-treatment failure (PP population)

Locoregional control rate (PP) **population)**



*p-value refers to TPF-CRT/ PF-CRT vs CRT





Safety:

	Induction period				Chemoradiotherapy period					
	TPF-CRT n=153		PF-CRT n=156		TPF-CRT n=106		PF-CRT n=114		CRT n=118	
Toxicity	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematologic										
Anemia	3 (2.0)	1 (0.7)	1 (0.6)	0 (0.0)	5 (4.7)	0 (0.0)	5 (4.4)	1 (0.9)	4 (3.4)	1 (0.9)
Thrombo-cytopenia	5 (3.3)	0 (0.0)	5 (3.2)	4 (2.6)	8 (7.6)	4 (3.8)	6 (5.3)	3 (2.6)	4 (3.4)	1 (0.9)
Neutropenia	9 (5.9)	20 (13.1)	41 (26.3)	13 (8.3)	25 (23.6)	7 (6.6)	19 (16.7)	4 (3.5)	18 (15.3)	6 (5.1)
Febrile neutropenia	6 (3.9)	20 (13.1)	1 (0.6)	2 (1.3)	4 (3.8)	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.9)
Leukopenia	14 (9.2)	10 (6.5)	4 (2.6)	2 (1.3)	12 (11.3)	4 (3.8)	14 (12.3)	1 (0.9)	11 (9.3)	3 (2.5)
Non-hematologic										
Venous thrombosis	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stomatitis	12 (7.8)	2 (1.3)	18 (11.5)	5 (3.2)	42 (39.6)	10 (9.4)	45 (39.5)	12 (10.5)	34 (28.8)	5 (4.2)
Nausea	5 (3.3)	0 (0.0)	2 (1.3)	0 (0.0)	3 (2.8)	0 (0.0)	4 (3.5)	0 (0.0)	5 (4.2)	1 (0.9)
Vomiting	9 (5.9)	1 (0.7)	3 (1.9)	0 (0.0)	5 (4.7)	0 (0.0)	4 (3.5)	0 (0.0)	8 (6.8)	2 (1.7)
Nephropathy	8 (5.2)	2 (1.3)	2 (1.3)	0 (0.0)	2 (1.9)	0 (0.0)	2 (1.8)	0 (0.0)	5 (4.2)	1 (0.9)
Infection	5 (3.3)	2 (1.3)	3 (1.9)	0 (0.0)	4 (3.8)	1 (0.9)	5 (4.4)	2 (1.8)	4 (3.4)	1 (0.9)
Diarrhoea	9 (5.9)	2 (1.3)	5 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Asthenia	15 (9.8)	1 (0.7)	8 (5.1)	0 (0.0)	7 (6.6)	0 (0.0)	7 (6.1)	0 (0.0)	4 (3.4)	0 (0.0)
Alopecia	3 (2.0)	0 (0.0)	2 (1.3)	0 (0.0)	1 (0.9)	0 (0.0)	3 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.7)	0 (0.0)	14 (11.3)	2 (1.8)	9 (7.6)	0 (0.0)
Hypokalemia	5 (3.3)	2 (1.3)	2 (1.3)	2 (1.3)	0 (0.0)	1 (0.9)	1 (0.9)	2 (1.8)	2 (1.7)	1 (0.9)
Hyponatremia	7 (4.6)	1 (0.7)	6 (3.9)	1 (0.6)	3 (2.8)	0 (0.0)	2 (1.8)	0 (0.0)	1 (0.9)	0 (0.0)
Decreased appetite	8 (5.2)	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.9)	0 (0.0)	7 (6.1)	1 (0.9)	2 (1.7)	0 (0.0)
Odynophagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	14 (13.2)	0 (0.0)	17 (14.9)	0 (0.0)	8 (6.8)	0 (0.0)
Dysphagia	2 (1.3)	0 (0.0)	2 (1.3)	0 (0.0)	9 (8.5)	0 (0.0)	6 (5.3)	0 (0.0)	5 (4.2)	0 (0.0)
Ototoxicity	1 (0.7)	0 (0.0)	2 (1.3)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)
Neurotoxicity	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.9)	0 (0.0)	3 (2.6)	0 (0.0)	2 (1.7)	0 (0.0)

There were reported a total of 13 deaths due to study treatment toxicity; 7 (4.6%), 4 (2.6%) and 2 (1.7%) from the TPF-CRT, PF-CRT and CRT alone arms, respectively.

Statistical methods:

It was assumed that the proportion of patients free of progression after two years would be 35% in the chemotherapy induction arms, with a 15% of difference compared to the control arm. Considering a 1% of loss-rate for each interval, α=0.05 (two-sided), and β=0.20 (power=80%); the number of patients to be enrolled, according to the log-rank test, would be 118 per arm.

Assuming that the proportion of patients free of progression after two years would be 40% in the TPF induction arm, with a 10% of difference compared to the PF induction arm, and considering a 25% of loss-rate for each interval, α=0.05 (two-sided), and β=0.20 (power=80%); the number of patients to be enrolled, according to the log-rank test, would be 160 per arm.

Therefore, in order to achieve the primary objective of the trial 160 enrolled patients should be required per induction treatment arm and 118 for the CRT alone arm (control arm).

Summary:

Population characteristics: In the PP population, TPF-CRT and PF-CRT significantly improved the median time-to-treatment failure (TTF) with respect to CRT alone (TPF-CRT vs CRT: HR, 0.700; 95%CI, 0.518 to 0.947; p=0.0205; PF-CRT vs CRT: HR, 0.743; 95%CI, 0.554 to 0.995; p=0.0463). In addition, the locoregional control (LRC) rate was higher in the ICT-CRT arms in comparison with CRT alone (TPF-CRT, 68.1%; PF-CRT, 62.1%; CRT, 51.7%; p=0.0348). In the intention-to-treat population non-significant differences were observed for efficacy between the study treatments.

Issue date: 11-Mar-2013